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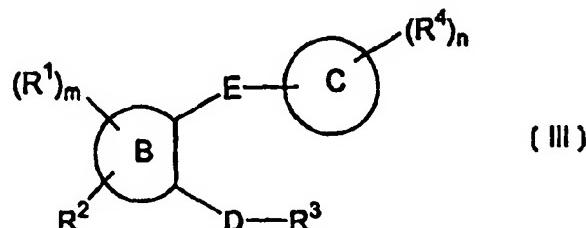
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(54) Title: *ORTHO-ANTHRANILAMIDE DERIVATIVES AS ANTI-COAGULANTS*

(57) Abstract

This invention is directed to compounds of formula (III) wherein B, C, D, E, R¹, R² and R³ are disclosed herein. These compounds are disclosed as being useful as anti-coagulants.



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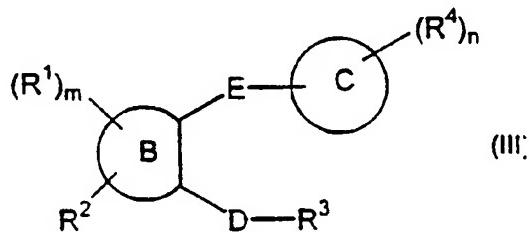
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AMENDED CLAIMS

[received by the International Bureau on 26 July 1999 (26.07.99);
Original claims 68 and 69 amended; remaining claims unchanged (8 pages)]

-C(O)OR⁵, -N(R⁵)R⁵ or -C(O)N(R⁵)R⁵), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶); or both R¹⁶'s together with the nitrogen to which they are attached (and wherein the R⁹ substituent is not present) form an aromatic N-heterocyclic ring containing zero to three additional hetero atoms, where the N-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)R⁵, -C(O)-(R⁸-O)-R⁵ (where t is 1 to 6), and -(R⁸-O)-R⁵ (where t is 1 to 6); each R¹⁷ is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, or -R⁸-C(O)-N(R⁵)R⁶; R¹⁸ is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR⁵, or -NO₂; and each R¹⁹ is cycloalkyl, haloalkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -R⁸-C(O)N(R⁵)R⁶, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶); as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

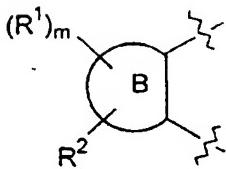
68.: Use of a therapeutically effective amount of a compound of formula (III):



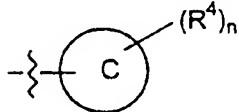
wherein

m is 1 to 3;

n is 1 to 5;



is an aryl or a heterocyclic ring substituted by R^2 and one or more R^1 groups;



is an aryl or a heterocyclic ring substituted by one or more R^4 groups;

D and E are independently a linker selected from the group consisting of $-N(R^5)-C(X)-$:

$-R^8-N(R^5)-C(X)-$; $-N(R^5)-C(X)-R^8-$; $-R^8-N(R^5)-C(X)-R^8-$; $-N(R^5)-S(O)_p-$; $-R^8-N(R^5)-S(O)_p-$

$-N(R^5)-S(O)_p-R^8-$; and $-R^8-N(R^5)-S(O)_p-R^8-$ (where p is 0 to 2; X is oxygen, sulfur or H_2)

where D and E can be attached to the B ring having the R^1 and R^2 substituents by either terminus of the linker;

each R^1 is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$

(where p is 0 to 2), $-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^5)R^6$, $-O-C(O)R^5$,

$-N(R^5)-CH(R^{12})-C(O)OR^5$, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo,

haloalkyl, o xo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$) or heterocyclylalkyl (optionally

substituted by alkyl, aryl, aralkyl, halo, haloalkyl, o xo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or

$-C(O)N(R^5)R^6$);

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2),

$-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-R^8-N(R^{10})R^{11}$,

$-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-S(O)_p-R^9$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^9$

(where p is 0 to 2), $-O-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-C(R^7)H-N(R^5)R^6$,

$-C(R^7)H-R^8-N(R^5)R^6$, $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$, $-O-R^8-N(R^{10})R^{11}$, $-O-R^8-O-C(O)R^5$,

$-O-R^8-CH(OH)-CH_2-OR^5$, $-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-(R^8-O)_t-R^{19}$ (where t is 1 to

6), $-O-R^8-C(O)R^5$, $-O-R^8-C(O)R^{19}$, $-O-R^8-C(O)OR^5$, $-N(R^5)-R^8-N(R^{10})R^{11}$,

$-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2), $-S(O)_p-R^8-C(O)OR^5$ (where p is 0 to 2), or

$-N(R^5)-CH(R^{12})-C(O)OR^6$;

R^3 is aryl or heterocyclyl both substituted by one or more R^{14} substituents independently selected from the group consisting of hydrogen, alkyl, halo, formyl, acetyl, cyano, $-R^8-CN$,

$-N(R^{10})R^{11}$, $-R^8-N(R^{10})R^{11}$, $-R^8-N^+(R^9)(R^{16})_2$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-OR^5$, $-R^8-OR^5$,

$-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2),

$-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-(R^8-O)_t-R^5$

(where t is 1 to 6), $-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-R^8-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$.

-C(R⁷)H-N(R⁵)-R⁸-[CH(OH)]-CH₂-OR⁵ (where t is 1 to 6), -C(R⁷)H-N(R⁵)-S(O)₂-N(R¹⁰)R¹¹, -C(R⁷)H-N(R¹⁰)-C(NR¹⁷)-N(R¹⁰)R¹¹, -C(R⁷)H-N(R¹⁰)-C(NR¹⁷)-R¹⁰, -C(NR¹⁷)-N(R⁵)R⁶, -C(R⁷)H-C(NR¹⁷)-N(R⁵)R⁶, -C(R⁷)H-O-N(R⁵)R⁶, heterocycl (wherein the heterocycl radical is not attached to the rest of the molecule through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), and heterocyclalkyl (wherein the heterocycl radical is not attached to the alkyl radical through a nitrogen ring and is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

each R⁴ is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, -C(O)N(R⁵)R⁶, or -R⁸-N(R⁵)R⁶;

each R⁵ and R⁶ is independently hydrogen, alkyl, aryl or aralkyl;

each R⁷ is independently hydrogen or alkyl;

each R⁸ is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R⁹ is independently alkyl, aryl or aralkyl;

each R¹⁰ and R¹¹ is independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, -R⁸-CN, -OR⁵, -R⁸-OR⁵, -S(O)_p-R¹⁵ (where p is 0 to 2), -R⁸-S(O)_p-R¹⁵ (where p is 0 to 2), -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -C(O)-R¹⁵, -C(O)NH₂, -R⁸-C(O)NH₂, -C(S)NH₂, -C(O)-S-R⁵, -C(O)-N(R⁵)R¹⁵, -R⁸-C(O)-N(R⁵)R¹⁵, -C(S)-N(R⁵)R¹⁵, -R⁸-N(R⁵)-C(O)H, -R⁸-N(R⁵)-C(O)R¹⁵, -C(O)O-R⁸-N(R⁵)R⁶, -C(N(R⁵)R⁶)=C(R¹⁸)R¹⁰, -R⁸-N(R⁵)-P(O)(OR⁵)₂, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR⁵), heterocycl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2), -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2), -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

or R¹⁰ and R¹¹ together with the nitrogen to which they are attached form a N-heterocyclic ring containing zero to three additional hetero atoms, where the N-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, -R⁸-CN, =N(R¹⁷), -OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)N(R⁵)R⁶, -R⁸-C(O)N(R⁵)R⁶, -N(R⁵)-N(R⁵)R⁶, -C(O)R⁵, -C(O)-(R⁸-O)-R⁵ (where t is 1 to 6), -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2), -(R⁸-O)-R⁵ (where t is 1 to 6), and heterocycl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,

-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶;

R¹² is a side chain of an α -amino acid;

each R¹⁵ is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R⁸-O-C(O)-R⁵, -R⁸-OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, heterocycl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶), or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶);

or R⁵ and R¹⁵ together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, OR⁵, -C(O)OR⁵, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R¹⁶ is independently alkyl, aryl, aralkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR⁵), heterocycl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶); or

both R¹⁶'s together with the nitrogen to which they are attached (and wherein the R⁹ substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)R⁵, -C(O)-(R⁸-O)_tR⁵ (where t is 1 to 6), and -(R⁸-O)_tR⁵ (where t is 1 to 6);

each R¹⁷ is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -C(O)-N(R⁵)R⁶, or -R⁸-C(O)-N(R⁵)R⁶;

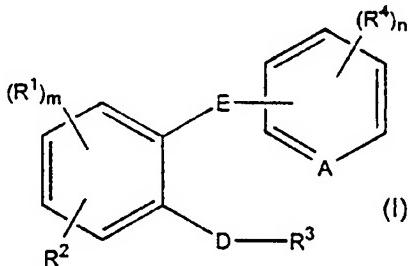
R¹⁸ is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR⁵, or -NO₂; and

each R¹⁹ is cycloalkyl, haloalkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -R⁸-C(O)N(R⁵)R⁶, heterocycl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof;

for the production of a medicament for the treatment of a human having a disease-state characterized by thrombotic activity.

69. Use of Claim 68, of a therapeutically effective amount of a compound of formula (I):



A is =CH- or =N-;

m is 1 to 3;

n is 1 to 4;

D is -N(R⁵)-C(Z)- or -N(R⁵)-S(O)_p- (where p is 0 to 2; Z is oxygen, sulfur or H₂; and the nitrogen atom is directly bonded to the phenyl ring having the R¹ and R² substituents);

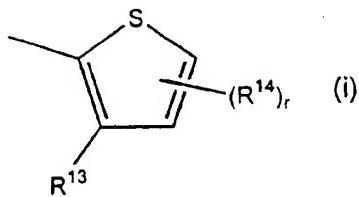
E is -C(Z)-N(R⁵)- or -S(O)_p-N(R⁵)- (where p is 0 to 2; Z is oxygen, sulfur or H₂; and the nitrogen atom can be bonded to the phenyl ring having the R¹ and the R² substituents or to the aromatic ring having the R⁴ substituent);

each R¹ is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -C(O)OR⁵, -C(O)N(R⁵)R⁸, -N(R⁵)R⁶, -O-C(O)R⁵, or -N(R⁵)-CH(R¹²)-C(O)OR⁵;

or two adjacent R¹'s together with the carbons to which they are attached form a heterocyclic ring fused to the phenyl ring wherein the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl and aralkyl;

R² is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -C(O)OR⁵, -C(O)N(R⁵)R⁶, -N(R¹⁰)R¹¹, -C(R⁷)H-N(R¹⁰)R¹¹, -C(R⁷)H-R⁸-N(R¹⁰)R¹¹, -C(R⁷)H-OR⁵, -C(R⁷)H-R⁸-OR⁵, -C(R⁷)H-S(O)_p-R⁹ (where p is 0 to 2), -C(R⁷)H-R⁸-S(O)_p-R⁹ (where p is 0 to 2), -O-R⁸-S(O)_p-R⁹ (where p is 0 to 2), -C(R⁷)H-N(R⁵)R⁶, -C(R⁷)H-R⁸-N(R⁵)R⁶, -O-R⁸-CH(OH)-CH₂-N(R¹⁰)R¹¹, -O-R⁸-N(R¹⁰)R¹¹, -O-R⁸-O-C(O)R⁵, -O-R⁸-CH(OH)-CH₂-OR⁵, -O-(R⁸-O)_tR⁵ (where t is 1 to 6), -O-(R⁸-O)_tR¹⁹ (where t is 1 to 6), -O-R⁸-C(O)R⁵, -O-R⁸-C(O)R¹⁹, -O-R⁸-C(O)OR⁵, -N(R⁵)-R⁸-N(R¹⁰)R¹¹, -S(O)_p-R⁸-N(R⁵)R⁶ (where p is 0 to 2), -S(O)_p-R⁸-C(O)OR⁵ (where p is 0 to 2), or -N(R⁵)-CH(R¹²)-C(O)OR⁵;

R³ is a radical of formula (i):



where:

r is 1 or 2;

R^{13} is hydrogen, alkyl, halo, haloalkyl, $-N(R^5)R^6$, $-C(R^7)H-N(R^5)R^6$, $-OR^5$, $-R^8-OR^5$,

$-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2) or heterocyclylalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, cyano, $-R^8-CN$, $-N(R^{10})R^{11}$,

$-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-R^8-N(R^{10})R^{11}$, $-C(R^7)H-N^{\oplus}(R^9)(R^{16})_2$,

$-C(R^7)H-R^8-N^{\oplus}(R^9)(R^{16})_2$, $-C(O)OR^5$, $-C(R^7)H-C(O)OR^5$, $-C(R^7)H-R^8-C(O)OR^5$,

$-OR^5$, $-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^{15}$ (where p is 0 to 2),

$-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-C(R^7)H-C(O)N(R^5)R^6$,

$-C(R^7)H-R^8-C(O)N(R^5)R^6$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6),

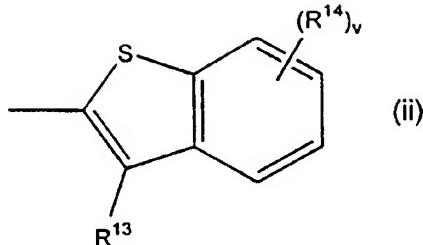
$-C(R^7)H-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-R^8-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$,

$-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is 1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$,

$-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, $-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-C(NR^{17})-N(R^5)R^6$,

$-C(R^7)H-O-N(R^5)R^6$, heterocyclyl (wherein the heterocyclyl radical is not attached to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (wherein the heterocyclyl radical is not attached to the alkyl radical through a nitrogen atom and is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^3 is a radical of the formula (ii):



where v is 1 to 4;

R¹³ is as defined above for formula (i); and

R¹⁴ is as defined above for formula (i);

each R⁴ is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, -C(O)N(R⁵)R⁶, or -R⁸-N(R⁵)R⁶;

R⁵ and R⁶ are each independently hydrogen, alkyl, aryl or aralkyl;

each R⁷ is independently hydrogen or alkyl;

each R⁸ is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R⁹ is independently alkyl, aryl or aralkyl;

R¹⁰ and R¹¹ are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, -R⁸-CN, -OR⁵, -R⁸-OR⁵, -S(O)_p-R¹⁵ (where p is 0 to 2), -R⁸-S(O)_p-R¹⁵ (where p is 0 to 2), -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -C(O)-R¹⁵, -C(O)NH₂, -R⁸-C(O)NH₂, -C(S)NH₂, -C(O)-S-R⁵, -C(O)-N(R⁵)R¹⁵, -R⁸-C(O)-N(R⁵)R¹⁵, -C(S)-N(R⁵)R¹⁵, -R⁸-N(R⁵)-C(O)H, -R⁸-N(R⁵)-C(O)R¹⁵, -C(O)O-R⁸-N(R⁵)R⁶, -C(N(R⁵)R⁶)=C(R¹⁸)R¹⁰, -R⁸-N(R⁵)-P(O)(OR⁵)₂, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR⁵), heterocycl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2), -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2), -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

or R¹⁰ and R¹¹ together with the nitrogen to which they are attached form a N-heterocyclic ring containing zero to three additional hetero atoms, where the N-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, -R⁸-CN, =N(R¹⁷), -OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)N(R⁵)R⁶, -R⁸-C(O)N(R⁵)R⁶, -N(R⁵)-N(R⁵)R⁶, -C(O)R⁵, -C(O)-(R⁸-O)_t-R⁵ (where t is 1 to 6), -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2), -(R⁸-O)_rR⁵ (where r is 1 to 6), and heterocycl (optionally substituted by one or

more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶;

R¹² is a side chain of an α -amino acid;

each R¹⁵ is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R⁸-O-C(O)-R⁵, -R⁸-OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶);

or R⁵ and R¹⁵ together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, -OR⁵, -C(O)OR⁵, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R¹⁶ is independently alkyl, aryl, aralkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR⁵), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶); or

both R¹⁶'s together with the nitrogen to which they are attached (and wherein the R⁹ substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)R⁵, -C(O)-(R⁸-O)_tR⁵ (where t is 1 to 6), and -(R⁸-O)_tR⁵ (where t is 1 to 6);

each R¹⁷ is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -C(O)-N(R⁵)R⁶, or -R⁸-C(O)-N(R⁵)R⁶;

R¹⁸ is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR⁵, or -NO₂; and

each R¹⁹ is cycloalkyl, haloalkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -R⁸-C(O)N(R⁵)R⁶, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, for the production of a medicament for the treatment of a human having a disease-state characterized by thrombotic activity.